REMARKS

Claims 48-49, 83-108 and 111-124 constitute the pending claims in the present application. Claims 48-49 have been withdrawn from consideration, claims 109-110 have been canceled, without prejudice, and claim 83 has been amended. The claim amendments are fully supported by the specification. No new matter has been introduced. Support for the amendments may be found, for example, at page 30, line 27 to page 31, line 8, etc.

Amendment of claims should in no way be construed as an acquiescence to any of the Examiner's rejections. The amendments to the claims are being made solely to expedite prosecution of the present application and do not, and are not intended to, narrow the claims in anyway. Applicants reserve the option to further prosecute the same or similar claims in the instant or in a subsequent patent application.

Applicants respectfully request reconsideration in view of the following remarks. Issues raised by the Examiner will be addressed below in the order they appear in the prior Office Action.

Priority

The Examiner asserts that the claims of the instant application do not receive the benefit of earlier applications PCT/US01/108435, 60/243,097 and 60/189,739 because it is alleged that the priority applications do not provide support for the claims. Therefore, the Examiner states that the claims are granted a priority date of January 22, 2002 based on the effective filing date of the instant application. Applicants respectfully disagree and submit that the currently pending claims are entitled to the priority date of at least March 16, 2001 based on the effective filing date of PCT/US01/08453. In particular, Applicants wish to direct the Examiner's attention to page 22, lines 4-19, page 11, lines 1-12, page 2, lines 16-22, page 3, lines 20-29, page 4, line 31 to page 5, line13, page 24, lines 10-31, etc. of PCT/US01/08435 (e.g., WO 01/68836) which is believed to provide sufficient support for the claims of the instant application. Additionally, Applicants reserve the right to claim the benefit of provisional applications 60/243,097 and 60/189,739 for all subject matter disclosed therein upon indication of allowable subject matter or upon application of an intervening reference.

Double Patenting

Claims 95-98 and 101 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being not patentably distinct over claims 25-28 of U.S. Patent Application No. 10/350,798. Applicants note that claims 25-28 of the '798 application were canceled by preliminary amendment filed on August 3, 2005. Accordingly, reconsideration and withdrawal of the double patenting rejection over claims 25-28 of the '798 application is respectfully requested.

The Claims Comply with 35 U.S.C. §112, first paragraph

Claims 83-108 and 111-124 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Applicants respectfully traverse this rejection.

As Applicants understand the rejection, the Examiner is asserting that the claim limitations "19 to 100 nucleotides" and "does not produce a general sequence-independent killing of the mammalian cells" is being objected to on the basis of new matter. Applicants respectfully disagree with the rejection, however, in an effort to expedite prosecution of the instant application claim 1 has been amended to recite "20 to 100 nucleotides." Applicants submit that the claims as currently pending are amply supported by the instant application as well as priority application PCT/US01/08435. For example, the Examiner's attention is directed to page 2, lines 27-31, page 3, line 32 to page 4, line 2, page 5, lines 8-9, page 5, lines 18-23, page 6, lines 6-14, page 19, line 8 to page 20, line 13, page 30, line 27 to page 31, line 8, page 32, line 34 to page 33, line 24, etc. of the instant application which are believed to support the currently pending claims. Support provided in priority application PCT/US01/08435 is detailed above. In particular, the Examiner's attention is directed to page 30, line 27 to page 31, line 8 which is believed to provide exemplary support for the limitation "20-100 nucleotides" and page 19, line 8 to page 20, line 13 which is believed to provide exemplary support for the limitation "does not produce a general sequence-independent killing of the mammalian cells." Support for these claim limitations may also be found in priority application PCT/US01/08435, for example, at page 22, lines 4-19 and page 11, lines

1-12. Accordingly, Applicants submit that the claims fully comply with the written description requirement under 35 U.S.C. § 112, first paragraph. Reconsideration and withdrawal of this rejection are respectfully requested.

Claim Rejections under 35 U.S.C. § 102(e):

Claims 83-88, 90-100, 102-108, 113-115, 120, 123-124 were rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Barber et al. (U.S. Patent No. 6,605,429). Applicants respectfully traverse the rejection.

Barber et al. is directed to ribozyme constructs. Ribozymes are enzymatic nucleic acids that contain two types of sequences (1) one or more sequences that bind to the target nucleic acid, and (2) sequences having secondary structure that form the catalytic core. Ribozyme sequences that bind to the target nucleic acid are not complementary to another sequence within the ribozyme. The structures of various classes of ribozymes are shown, for example, in Figure 2 of Exhibit A (Tang and Breaker, Proc. Natl. Acad. Sci. USA 97: 5784-5789 (2000); attached hereto) and Figure 1 of Barber et al. As shown in the figures, the ribozymes contain sequences that bind to the target sequence (or substrate) and sequences that contain secondary structure and form the catalytic core. However, the ribozymes do not contain sequences that both bind to the target sequence and which are complementary to another sequence within the ribozyme molecule. In contrast to ribozymes, the present claims utilize a hairpin RNA comprising self complementary sequences that form duplex regions *and* which hybridize to the target gene. The hairpin RNAs of the instant application therefore comprise sequences that are complementary to both the target gene and another sequence within the hairpin RNA molecule itself. As such the hairpin RNAs of the instant application are distinct from the ribozyme molecules described in Barber et al.

Accordingly, Barber et al. fails to teach or suggest a method for attenuating gene expression using a hairpin RNA comprising self complementary sequences that form duplex regions *and* which hybridize to a target gene. The standard for anticipating a claim is clearly outlined in MPEP 2131, and this standard is further supported by the Courts. "A claim is anticipated only if each and every element as set forth in the claim is

found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1978). "The identical invention must be shown in as complete detail as is contained in the claim." *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). In sum, Barber et al. do not disclose all the limitations of the present claims as amended and thus fail to anticipate the claimed subject matter. Reconsideration and withdrawal of this rejection under 35 U.S.C. § 102(e) are respectfully requested.

Claim Rejections under 35 U.S.C. § 103(a):

Claims 83-87, 95-98, 102-108, 111-115, 120-124 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Fire et al. (U.S. Patent No. 6,506,559) in view of Agrawal et al. (WO 94/01550) and as evidenced by Tuschl et al. (US 2004/0229266). Applicants respectfully traverse the rejection.

Applicants respectfully disagree with the rejection and note that pursuant to MPEP 2142, "To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicants' disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)."

As discussed above, Applicants submit that the currently pending claims are entitled to a priority date of at least March 16, 2001 based on the filing date of priority application PCT/US01/08453. Accordingly, Applicants submit that Tuschl et al. is not properly cited as a reference against the instant application as the filing date of Tuschl et al. is after the priority date of the currently pending claims. To the extent the rejection is maintained on the basis of Fire et al. and Agrawal et al. alone, Applicants provide the remarks set forth below.

First, Applicants submit that there is no motivation to combine the teachings of Fire et al. with the teachings of Agrawal et al. The Examiner asserts that it would have been obvious to use an oligonucleotide of 19-100 nucleotides in length based on the disclosure of Agrawal et al. in association with the dsRNAs taught by Fire et al. However, Fire et al. is directed to dsRNAs that act through an RNA interference mechanism while Agrawal et al. is directed to antisense oligonucleotides. One of skill in the art would have readily understood that the mechanism of action of antisense oligonucleotides is distinct from an RNA interference mechanism. As such, there would be no reason to believe that the structural requirements for antisense oligonucleotides would be applicable to dsRNAs useful for RNA interference.

Agrawal et al. is directed to antisense constructs and does not teach or suggest nucleic acid constructs useful for producing RNA interference. To that end, Agrawal et al. states, in the Summary of the Invention, "oligonucleotides according to the invention form stable hybrids with target sequences under physiological conditions, *activate RNase H* and produce only nucleosides as degradation products.....This results in oligonucleotides that activate RNase H, *an important feature for the antisense therapeutic compound*" (emphasis added). Likewise, the Detailed Description section of Agrawal et al. sets forth the requirements of the antisense construct as follows: "the invention provides therapeutic self-stabilized oligonucleotides that are *more resistant to nucleolytic degradation* than oligonucleotides that are known in the art", and "the invention provides nuclease resistant oligonucleotides that *activate RNase H*" (emphasis added).

RNase H degrades the RNA of DNA-RNA hybrids. As Agrawal et al. recognizes, this is an important requirement for antisense constructs. However, RNase H does *not* degrade single-stranded nucleic acids, duplex DNA or double-stranded RNA. Thus, to the extent Agrawal teaches stabilized duplexes including RNA, those complexes must also include some further feature rendering them capable of activating RNase H. That is, in contrast to the hairpin RNA constructs of the pending claims, the stabilized hairpin constructs of Agrawal et al. cannot be ribonucleic acids alone.

In contrast, the hairpin RNAs of the pending claims do not work by a mechanism that would include activation of RNase H, and are specifically required to be susceptible

to nucleolytic cleavage, e.g., as they must be substrate for cleavage by an RNase III enzyme.

In addition to these distinctions between the mechanisms of RNA interference and antisense oligonucleotides, Applicants note that the Fire et al. reference itself distinguishes between the dsRNAs disclosed therein and antisense oligonucleotides. For example, Fire et al. details the distinctions between antisense RNA and RNA interference at column 3, lines 19-34. Additionally, the data presented in Fire et al. indicates that purified sense or antisense oligonucleotides when administered alone had little to no effect. However, upon mixing and preannealing the sense and antisense oligonucleotides to form a dsRNA molecule, significant effects were obtained (see e.g., column 15, lines 44-49, column 21, lines 19-35, Figure 4, and Table 1 at columns 21-24, etc.). The teachings of Fire et al. therefore provide direct evidence that an antisense oligonucleotide and a dsRNA having the same length and targeted to the same sequence show very different activities. Accordingly, there would be no basis to believe that structural characteristics, such as length, useful for antisense oligonucleotides would be useful or applicable for dsRNAs that operate through an RNA interference mechanism. As such, there is no motivation to combine the teachings of Agrawal et al. with the teachings of Fire et al.

Second, Applicants submit that there is no reasonable expectation of success for achieving gene attenuation in mammalian cells using a hairpin RNA based on the disclosures of Fire et al. and Agrawal et al. In particular, Applicants submit that Fire et al. is not enabling for a method of inhibiting expression of a target gene in *mammalian* cells. In order for those skilled in the art to reasonably believe that a double stranded RNA could induce sequence-specific gene silencing, they first needed to understand the cellular mechanism of this biological phenomenon. At the time Fire et al. was filed in 1998, that mechanism was not known to the public nor described in Fire et al. although procedures based on double stranded RNA-triggered silencing were fairly well-established tools for functional genomics of lower organisms (plants, invertebrates and fungi). Nevertheless, the simple protocols used for invertebrate and plant systems were not effective in mammalian cells at that time. Indeed, a reference by Fire (an inventor of the '559 patent) published after the filing date of the '559 patent, provides

evidence that the '559 patent was not enabled for gene attenuation in mammalian cells (Fire, *Trends in Genetics*, 15: 358-363 (1999)[1]):

> Procedures based on RNA-triggered silencing are now well-established tools for functional genomics of lower organisms (plants, invertebrates and fungi). Valuable information about gene function can be obtained, even in cases where only a partial loss-of-function is generated. From a technical perspective, one could certainly hope that RNA-triggered silencing would exist in vertebrates: this would facilitate functional genomics and might allow medical applications involving targeted gene silencing of 'renegade' genes. Although this hope is not ruled out by any current data, the simple protocols used for invertebrate and plant systems are unlikely to be effective. Mammals have a vehement response to dsRNA, the best-characterized component of which is a protein kinase (PKR) that responds to dsRNA by phosphorylating (and inactivating) translation factor EIF2a.*** (Fire, *supra* at page 362-363)

Thus, in the absence of the biochemical and genetic approaches carried out by the inventors in several experimental systems and described in the instant application, those skilled in the art would have had no reasonable expectation that, based on the teachings of Fire et al., double stranded RNAs would have any effect as a gene silencing agent in mammalian cells.

Furthermore, Agrawal et al. provides no basis for overcoming the deficiencies of Fire et al. In particular, Agrawal et al. provides no teachings that would lead one skilled in the art to have a reasonable expectation that double stranded RNAs would be effect for achieving gene attenuation in mammalian cells.

In sum, there is no motivation to combine the teachings of Fire et al. with the teachings of Agrawal et al. given the mechanistic differences between antisense oligonucleotides and RNA interference. Additionally, there would have been no reasonable expectation of success for achieving gene attenuation in mammalian cells using dsRNAs in view of the Fire publication from 1999. Accordingly, Fire et al. and Agrawal et al. taken alone or in combination fail to teach or suggest each and every element of the claimed invention and therefore fail to render the pending claims obvious.

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[1] Cited as Reference AU on the Information Disclosure Statement filed in association with the instant application on May 30, 2003.

Reconsideration and withdrawal of rejection under 35 U.S.C. § 103(a) are respectfully requested.

Claims 83-108, 113-115, 120, 123-124 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Barber et al. (U.S. Patent No. 6,605,429) in view of Good et al. (Gene Therapy 1997) Lipardi et al. (Cell 2001) in further view of Bennett et al. (US Patent No. 5,998,148) and as evidenced by Hammond et al. (Nature 2000). Applicants respectfully traverse the rejection.

As discussed above, Applicants submit that the currently pending claims are entitled to a priority date of at least March 16, 2001 based on the filing date of priority application PCT/US01/08453. Accordingly, Applicants submit that Lipardi et al. is not properly cited as a reference against the instant application as the publication date of Lipardi et al. is after the priority date to which the currently pending claims are entitled. Additionally, Applicants submit that the Hammond et al. reference is co-authored by the co-inventors of the instant application. Since Applicants believe that the currently pending claims are entitled to an effective filing date of March 16, 2001, the Hammond et al. reference may be addressed as a publication of Applicant's own work in accordance with MPEP §715.01(c). Therefore, Applicants will not address the Hammond et al. reference until the priority date to which the instant claims are entitled has been established. To the extent the rejection is maintained on the basis of Barber et al., Good et al. and Bennett et al., Applicants provide the remarks set forth below.

To establish a *prima facie* case of obviousness, the prior art reference (or references when combined) must teach or suggest all the claim limitations. As outlined in greater detail above, Barber et al. fails to teach or suggest the methods of the currently pending claims. In particular, the claims of the instant application are directed at least in part to a method for attenuating gene expression using a hairpin RNA comprising self complementary sequences that form duplex regions *and* which hybridize to a target gene. However, Barber et al. fails to teach or suggest such hairpin RNAs. Barber et al. is directed to ribozymes which contain two types of sequences (1) one or more sequences that bind to the target nucleic acid, and (2) sequences having secondary structure that form the catalytic core. In contrast to the hairpin RNAs of the instant application,

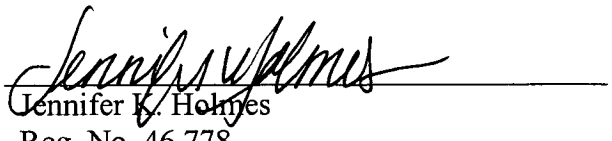
ribozymes do not contain sequences that both bind to the target sequence and which are complementary to another sequence within the ribozyme molecule. The structure of the ribozymes disclosed in Barber et al. are therefore distinct from the structure of the hairpin RNAs described in the instant application.

The Examiner relies on Good et al. for teaching an expression construct comprising a U6 promoter and Bennett et al. for teaching targeting of non-coding regions of a target gene. However, such teachings fail to make up for the deficiencies of Barber et al. In particular, no combination of Good et al., Bennett et al. or Barber et al. teaches or suggests a method for attenuating gene expression using a hairpin RNA comprising self complementary sequences that form duplex regions and which hybridize to the target gene. Accordingly, reconsideration and withdrawal of rejection under 35 U.S.C. § 103(a) are respectfully requested.

CONCLUSION

The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should any additional extensions of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to Deposit Account No. **18-1945**, under Order No. CSHL-P03-010 from which the undersigned is authorized to draw.

Respectfully Submitted,



Jennifer K. Holmes
Reg. No. 46,778

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Customer No: 28120
Docketing Specialist
Ropes & Gray LLP
One International Place
Boston, MA 02110
Phone: 617-951-7739
Fax: 617-951-7050